REMARKS

Status of the Application and Request to Rejoin Withdrawn Claims

Claims 20-24, 27-30, 33, and 49-61 are currently pending in this application. Of those, claims 20-24, 27-30, and 33 are withdrawn and claims 49-61 are under examination.

Applicants continue to request rejoinder of the withdrawn claims, as they are all dependent upon the elected thrombin preparations of claim 49 and are drawn to processes of producing such preparations. Therefore, Applicants may re-join all of the withdrawn claims as a matter of right once claims 49-61 are deemed allowable. *See* M.P.E.P. § 821.04.

The only amendment presented herein is the correction of a typographical error in claim 49. The previous amendment mistakenly deleted the word "buffer" prior to the word "substance" in that claim. The instant amendment corrects that error. Applicants respectfully request the entry of that amendment.

Claims 49-61 Are Enabled

The Office first rejects claims 49-61, contending that claim 49 is not enabled throughout its full scope. (Office Action at pages 2-3.) Applicants traverse this rejection.

Before discussing the substance of the Office's rejection, Applicants first note that this issue has already been raised and overcome in earlier prosecution. (See the Final Rejection of November 28, 2003, the Appeal Brief filed May 19, 2004, and the Examiner's Answer mailed July 29, 2004, in which an enablement rejection on similar or the same grounds as here was made by the Examiner and overcome by Applicants.) It

is the Office's own policy to avoid piecemeal prosecution. M.P.E.P. § 707.07(g). Accordingly, it is needlessly burdensome to both the Office and Applicants to re-reject claims based on assertions that have already been satisfactorily addressed.

Furthermore, this enablement rejection is not a *prima facie* case because it is based on far too stringent a standard. The Office contends that the claims are only enabled for thrombin preparations containing the specific additives mentioned in the claims or working examples of the specification but not for thrombin preparations containing an "amino acid" or a "sugar" more generally, for example. (Office Action at page 2.)

In addition, the Office supports its assertions only by general, conclusory statements such as "biotechnology is a highly unpredictable art" rather than with the substantive evidence based on factual, scientific reasoning which the Office is required to provide. *See In re Zurko,* 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001); *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). In any case, predictability or lack thereof is not the test of enablement. Instead, the test of enablement is whether the experimentation needed to practice the invention as claimed is "undue." M.P.E.P. § 2164.

The experimentation in this case is not undue for the reasons the Office has already considered and found persuasive. (See the parts of the prior prosecution cited above.) Further, determining whether or not the level of experimentation needed to carry out an invention is "undue" involves many factors of which predictability is only one.

The seminal case of *In re Wands*, 858 F.2d 731, 737-8, cited in the M.P.E.P. at § 2164.01 provides a classic example of an enabled invention in a biotechnology field

the court considered potentially unpredictable – that of a monoclonal antibody for a particular antigen. The court acknowledged in *Wands* that the methods required to make hybridoma cells at the time of the invention were complicated and time-consuming and that the outcome of screens to find the claimed monoclonal antibodies would not be predictable. But, the court recognized that, despite its unpredictability, hybridoma technology involves a series of routine procedures and that the specification provided sufficient directions for one to proceed. Thus, the court's opinion emphasized that, even in an unpredictable art, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 8 U.S.P.Q. at 140 (citations omitted).

The techniques involved in determining if a given thrombin preparation meets the claimed functional requirements of claim 49 are also relatively routine and involve thrombin activity tests described in the working examples of the application conducted before and after storage. The Office has not met its burden to explain why it believes such procedures would allegedly be undue to one of ordinary skill.

Moreover, the issue of the metes and bounds of the thrombin inhibitor, sugar, amino acid, etc. under claim 49 has been raised and dispensed with in earlier prosecution. (See documents cited above.) In any event, it would not require undue experimentation to make and use the thrombin preparations of claim 49, even if one must first test additives from among the claimed list to determine whether they fall within the functional limitations of the claim.

As the case of *In re Angstadt* illustrates, generic claims in an unpredictable art are even allowed to encompass a certain number of inoperative embodiments. 537 F.2d 489, 190 U.S.P.Q. 214 (C.C.P.A. 1976). At issue in *Angstadt* was whether a claim generically reciting a "catalyst" was enabled, or whether only the specific catalysts used in the patent's text were enabled. As the court explained, "[t]he question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with ***every*** species covered by the claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts . . . such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed." 190 U.S.P.Q. at 218 (emphasis in original) (footnote omitted). In *Angstadt*, as here, the patent's disclosure was sufficient to point an experimenter toward appropriate ingredients falling within the generically claimed class.

For all of the above reasons, this ground of rejection should be withdrawn.

Claims 49-61 Have Written Description Support

The Office yet again insists that claims 49-61 lack support in the application as filed under 35 U.S.C. § 112, first paragraph. (Office Action at pages 4-5.) Applicants again traverse that rejection.

Written description support does not require literal, word-for-word, recitation in the descriptive text. Instead, the specification may also implicitly or inherently support

the claims, such as through the figures, the data in the working examples, and in the more general statements of the text. M.P.E.P. § 2163.02; *and see, e.g., Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC,* 72 U.S.P.Q.2d 1190, 1199 (Fed. Cir. 2004) (a claim element reciting that the thickness of one part of a structure was wider than another part of the structure was sufficiently supported in the application because the relative widths in question could be seen from one of the figures, though they were not described in words).

But this application actually does provide literal or nearly literal, word-for-word support for many if not most of the claim terms that the Office objects to. Such support is far more than is required under 35 U.S.C. § 112.

Nonetheless, to advance prosecution, Applicants reiterate the portions of the application that provide support for the rejected phrases, which, in many cases is nearly word-for-word support, and request the Office to consider them.

1. "after at least 12 [24] months of storage at 20-25 °C in the liquid state, the thrombin activity of the preparation, measured by a coagulation test with a fibrinogen substrate, is more than 70% [80%] of its initial level prior to the storage"

The above claim limitations are supported at several places in the application, notably in Table 5, where such results are actually reduced to practice. (See the application at page 15, columns 8 and 9, % stability at 12 and 24 months of storage at 20-25 °C.) The specification at page 3, lines 8-9, and page 6, entire page, also supports the above claim limitations almost literally.

Applicants first note that the Office does not make out a *prima facie* case of unpatentability supported by the required substantial evidence standard. First, the

Office agrees with Applicants that the "specification supports for '12 months or more.' But, then the Office states that the specification "does not support ranges below that." (Office Action at page 4.) Applicants do not understand what the Office means by "ranges below that" as all of the claimed ranges are for 12 months or greater, not for less than 12 months. In any event, if the Office means to challenge the support for the 24-month limitation, Applicants direct the Office's attention to Table 5 which provides a demonstration of two claimed species with more than 80% of the initial thrombin activity at 24 months of storage.

The Office also comments that "the specification states that the thrombin activity is over 70-80% of the initial level. In other words, 70-80% over less than what was initially measured. Applicant has taken this to mean more than 70-80% but that is not what the specification says." (*Id.*) Again, Applicants fail to understand the Office's reasoning here. As a matter of simple English usage, "**over** 70-80% of the initial level" means exactly the same thing as **more than** 70-80% of the initial level, as Applicants in fact claim. Hence, the Office should acknowledge support for that claimed thrombin activity under the recited time periods, in line with its recognition that the specification literally supports that limitation.

In any event, Applicants urgently request the Office to recall that literal word-for-word support is not the standard by which written description is judged. However, when such nearly literal support is actually provided, which it is here, the Office should withdraw a rejection based on lack of support. Otherwise, if minor alterations of the claimed language are all that the Office is requesting by its comments above, the

Examiner is invited to contact Applicants' representatives so that prosecution may advance.

2. "more than 90% of the initial level"

The Office again contends that the language "more than 90%" in claims 51 and 54 is not shown in the specification. However, as Applicants have previously mentioned, that limitation is inherently supported by the data in Table 5. In that table, the stability values of two exemplary preparations according to the invention, after storage for 12 months at the claimed temperature range, are 100.9% and 90.6%. Thus, those two examples are "more than 90%" stable after 12 months. (See the application at page 15, preparations 8 and 9.) Further, one of the two preparations has a thrombin activity of 90.1% after 24 months, and thus is certainly "more than 90%" stable after 24 months. (See *Id.*) Again, literal word for word support of a claim language is not the correct standard by which to judge compliance with the written description requirement. Instead, there are a variety of ways to show support for a claim limitation, including by demonstrating the claimed limitations through results in a table of data. See, e.g., M.P.E.P. § 2163; *Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC,* 72 U.S.P.Q.2d 1190, 1199 (Fed. Cir. 2004).

Specific numerical ranges may also be inherently supported by data in an application. For example, in the case of *In re Wertheim*, working examples showing 36% and 50% of a particular ingredient within a claimed composition, coupled with a written disclosure of a range of 25% to 60%, was found sufficient to support a claimed range of 35% to 60%. M.P.E.P. § 2163.06(III); 191 U.S.P.Q. 90, 93-97 (C.C.P.A. 1976). In other words, disclosure of a value of 35%, approximating the claimed end point of

36% was sufficient support for the claim. Similarly here, particular examples of the claimed preparations that retain 90.1% or 90.6% or 100.9% of their original stability after the claimed time periods and at the claimed temperature range also inherently support claims drawn to a range of "more than 90%."

Finally, those three values in the Table 5 stand out in comparison to the other data because they derive from the only exemplary preparations that contain all of the ingredients required by claim 49. Hence, one of ordinary skill in the art would certainly conclude that Applicants possessed and clearly disclosed the features of claims 51 and 54.

Therefore, in continuing to ask for written statements to support the claim language, Applicants can only conclude that the Office is not applying a proper test for written description support.

3. "Sugar alcohol at a maximum of 2%"

Finally, the Office once again objects to the requirement in claim 58 for "sugar alcohol at a maximum of 2%" first because, in the Office's opinion, "no where in the specification does it ever suggest that one can only use the sugar alcohols at a maximum concentration of 2%." (Office Action at page 5.) Applicants note that claim 58 is a dependent claim. Certainly, under claim 49, higher amounts of sugar alcohols could be used if desired. However, there is support in the application, as the Office notes, for either no sugar alcohol (such as when another additive is selected instead), 1% sugar alcohol, or 2% sugar alcohol, for example. (See Table 4, at page 12, and claim 49.) In other words, there is support for a range of sugar alcohol from zero to 2%, just as claim 58 covers.

Second, referring to Table 4 at page 12, the Office implies that the application supports only mannitol at that concentration range. (Office Action at page 5.) Applicants submit that the standard the Office is applying here is far too high.

In this case, the use of mannitol in Table 4, is merely a working example. The application as a whole directs those of ordinary skill in the art that the concentration range which works for mannitol could be used with sugar alcohols generally, for example, glycerol. (*See, e.g.,* original claim 8 generally reciting "sugar alcohols.")

Further, the M.P.E.P. explains that an example species supports claims to a genus so long as the behavior of other members of the genus is reasonably predictable based on that of the disclosed species. *See* M.P.E.P. § 2163.05(I)(section entitled: Addition of a Generic Claim). Here, the Office has provided no evidence to suggest that there is anything unique about mannitol and that other sugar alcohols would not behave similarly. Hence, Applicants submit that the Office's rejection of claim 58 must be in error. The working examples and remaining original disclosure more than adequately support claim 58.

In light of all of the above remarks, Applicants respectfully request the Office to withdraw all of the written description rejections under 35 U.S.C. § 112, first paragraph.

Claims 49-61 Are Novel

Next the Office contends that the claims are anticipated by Griffin et al. (U.S. Patent No. 5,288,612; "Griffin"). (Office Action at page 5.) Applicants also traverse that rejection.

Griffin as a whole does not relate to preparing thrombin, but to preparing antibodies against protein C and to detection methods using those antibodies. The only

link to thrombin is that protein C is a protease that activates thrombin *in vivo*. Nevertheless, the Office points Applicants' attention to the example at col. 23-24 of the Griffin patent in which a protein C sample is tested for its ability to activate thrombin during a stage of its purification. The Office contends that that disclosure anticipates the claimed thrombin preparations. However, a careful reading of that example does not support such a conclusion.

To assist the Office, Applicants walk through the steps of that protein C preparation and the composition of the samples involved in order to show why there is no anticipation from Griffin. The example begins with a commercial Factor IX concentrate, which is of course a different protein from thrombin. Protein C is purified from that concentrate by chromatography on DEAE-Sephadex and eluted in a buffer that contains sodium chloride, sodium phosphate, EDTA, benzamidine hydrochloride, DFP, and sodium azide. (Griffin at col. 23, lines 34-48.) Fractions from that elution were then taken to see if the purified protein C activated thrombin using an APTT assay. (*Id.* at col. 23, line 66, to col. 24, line 6.) Even if one stops the analysis there and considers what ingredients are present in the thrombin activity test of the protein C purification, not all of the ingredients required by claim 49 are present. For instance, there is no "sugar, sugar alcohol, amino acid, salt of a mono- or polycarboxylic acid, or salt of a mono- or polyhydroxycarboxylic acid" in that solution. Furthermore, given the large concentration of protein C, which is a protease known to cleave thrombin, it is not clear that the activity assay would be considered a stable preparation of thrombin.

Continuing forward, after the elution described above, the protein C is then dialyzed into a buffer containing MES-Tris, benzamidine hydrochloride, calcium

chloride, and sodium azide. Then, another chromatography step is performed, changing the buffer to MES-Tris, benzamidine hydrochloride, calcium chloride, and sodium chloride, followed by a final buffer change to Tris, glycine, and EDTA. No thrombin is added to the protein C preparation at any of those later steps. Hence, they are all inapplicable to the instant invention.

Hence, there can be no anticipation because Griffin does not meet each and every claim limitation, as is an absolute requirement for a rejection under 35 U.S.C. § 102. Thus, Applicants request the withdrawal of this rejection.

Claims 49-61 Are Nonobvious

The Office also rejects the claims for alleged obviousness under 35 U.S.C. § 103(a) on several grounds. Applicants traverse all of those rejections.

1. Rejection over Griffin in view of Allary, Lorne, Hanada, and Altshuler

First, the Office rejects all of claims 49-61 as allegedly obvious over Griffin in view of several other patents or articles cited in prior prosecution. (Office Action at pages 6-7; Lorne et al. *Rev. Fr. Transfus. Hemobiol.* 32: 391-400 (1989); Allary et al. *Ann. Pharmaceutiques Francaises* 48: 129-35 (1990); United States Patent No. 5,945,103 to Hanada et al.; Brezniak et al., *Blood Coag. and Fibrinolys.* 5: 847-8 (1994); and United States Patent No. 4,363,319 to Altshuler.) The main basis for this rejection seems to be the Office's conclusion that Griffin anticipates the claims. (The teachings of the other materials in the combination are discussed in the sections that follow.)

However, as Applicants have just explained, Griffin cannot anticipate any of claims 49-61. Moreover, Griffin is not an appropriate reference for an obviousness rejection. It is neither in the field of an applicant's endeavor, nor does it relate directly

either to thrombin or to stabilized protein preparations. See § 2141.01(a) of the M.P.E.P. Instead of relating to stabilizing thrombin, Griffin deals with antibody-based diagnostic methods for detecting protein C levels. One of ordinary skill in the art would not look to such a document to find a solution to how to obtain a thrombin preparation with a long shelf life at room temperatures.

Hence, this rejection must be withdrawn.

2. Rejection of Claims 49-61 over Allary or Lorne in view of Hanada, Brezniak, and Altshuler

The Office next rejects all of the elected claims over Allary or Lorne in view of Hanada, Brezniak, and Altshuler. (Office Action at pages 7-11.) Applicants continue to traverse that rejection.

Again, a *prima facie* case of obviousness must meet the following three requirements: (1) all of the claim limitations must be taught or suggested; (2) there must be an objective teaching in the prior art, and not in the applicant's disclosure, to combine or modify the art; and (3) the prior art must teach a reasonable expectation of success in performing that combination or modification. (*See* M.P.E.P. §§ 2141-2143.) This rejection does not meet any of the above requirements. Thus, it is not a *prima facie* case.

First, none of the cited literature above actually teaches the long-term stability properties of claim 49. Nonetheless, the Office here concludes that the cited art inherently would meet all of the functional limitations of Applicants' claims. The Office's reasoning is that "percentages of activity of the enzyme are inherent to that enzyme, thus the conditions of the claims are inherent to the preparation." (Office Action at page

8.) However, one cannot assume that every preparation containing the ingredient mix of claim 49 will necessarily satisfy the stability criteria of claim 49.

Moreover, a prior art reference may be used to support an obviousness rejection only for what it objectively teaches to those of ordinary skill. It is not correct to base obviousness rejections on inherent properties unless those properties are actually taught or suggested in the art itself when that art is taken as a whole. *See* M.P.E.P. § 2143.03. As the courts have long explained, obviousness must be based only on properties that are actually known before the application is filed. But inherent properties, by definition, are usually unknown. Something that is unknown cannot be obvious. *See In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 757 (C.C.P.A. 1977), citing *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966) (emphasis added).

Therefore, any obviousness rejection that is improperly based on an unknown and un-taught inherent property is not a *prima facie* case and must be withdrawn.

That is the case here, because none of the five cited publications taken alone or in combination suggests that a thrombin preparation could be made more than 70% stable for over 12, or even 24 months, at 20-25 °C using the specific set of ingredients claimed here. In addition, none of the five publications suggests that one could achieve the heightened stability recited in claims 50-54 using the materials claimed. Nor do any of the publications suggest that it is possible to achieve the claimed levels of stability while at the same time preventing a viscosity increase as taught by claim 59, for example.

Due to those defects, the cited combination does not objectively teach or suggest all of Applicants' claim limitations, and thus fails the first requirement of a *prima facie* case of obviousness.

The cited combination also fails the second requirement: motivation to combine the teachings of the cited art.

In order to find a motivation to combine publications, there must be an objective suggestion or desire within the prior art itself to make the necessary modifications. *See, e.g., Winner Int'l. Realty Corp. v. Wang,* 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000). Even if a modification is theoretically possible or even if the general ingredients necessary are readily available, the prior art must still set forth an objective wish or desire for the specific changes embodied by the claims. *See* M.P.E.P. § 2143.01; *and see In re Gordon,* 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). For instance, a combination showing only that the claimed composition is one of many possibilities or trade-offs is not sufficient. *See Winner v. Wang*, 53 U.S.P.Q.2d 1580; *and see* M.P.E.P. § 2143.01. Instead, as the Federal Circuit has repeatedly explained, "particular findings must be made as to why one of ordinary skill in the art, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Lee,* 61 U.S.P.Q.2d at 1433 (quoting *In re Kotzab,* 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

Here, the Office cites a collection of different papers which, in combination, would actually push one of ordinary skill in a different direction from the claims. Applicants' claim 49, for example, requires a preparation having a specific minimum level of thrombin activity after a particular period of storage, and which comprises a

noncovalently binding inhibitor of thrombin activity, at least one soluble calcium salt, sodium chloride, at least one buffer substance and at least one other ingredient chosen from a specific list. Compared to those claimed ingredients and properties, three of the documents the Office cites actually direct those of ordinary skill away from using noncovalent inhibitors of thrombin activity for thrombin storage. The other two publications make no mention of such inhibitors.

At best, the five articles merely show that different ingredients used in Applicants' claimed preparations were available to those of ordinary skill in the art at the time of this invention, but they do not demonstrate that those of ordinary skill in the art would have known to select the specific set of ingredients that Applicants chose. And certainly, the set of articles does not suggest that by selecting the particular ingredients that Applicants claim, one would be able to keep thrombin stable over the long periods of time at high temperatures according to the instant claims. Instead, the prior art as a whole indicates that those of ordinary skill struggled to find ways to keep thrombin stable even in the face of the teachings the Office has cited here.

Thus, the instant combination also fails to meet the second requirement for a *prima facie* case.

Third, the five cited publications do not suggest that one should store thrombin solutions for the long term in the specific set of ingredients claimed here. Hence, those publications, in light of the prior art as a whole, also provide no reasonable expectation that thrombin would retain more than 70% of its activity when stored in Applicants' claimed solutions, let alone more than 80% or more than 90%.

Further, in considering claim 59, for example, the art prior to Applicants' invention taught that in order to achieve a thrombin preparation that is stable over the long term, that preparation should be stored in a viscous solution with high concentrations of polyols such as, for example, 10% or more of glycerol. (See the specification at page 3, lines 11-14.)

For instance, Altshuler teaches solutions with 30% glycerol or 15% mannitol and/or another highly viscous additive such as polyethylene glycol. (*See* Altshuler at col. 6, Examples I and II, and col. 8, line 64, to col. 9, line 2.) But even those solutions may not be stable beyond 8 months at 22 °C. (*Id.* at col. 9, lines 28-37.) European Patent Publication No. 0 221 700 A2 also teaches using 25% (w/w) glycerol or other "high concentrations of polyols" to stabilize thrombin preparations. (*See Id.* at page 1, line 26, and pages 4-5, Tables III and IV.) Some of the resulting preparations lost 29% of their activity within the first 41 days at 25 °C.

Claim 59, in contrast, requires that the concentration of the additives is low enough (e.g. 1-2% polyol) such that those ingredients do not increase the viscosity of the preparation. Yet, at the same time, the preparation of claim 59 is required to retain more than 70% of its original thrombin activity at essentially room temperatures over a period of at least one year. The art on thrombin preparations, as shown above, does not suggest that such a result would be feasible.

Thus, in summary, the Office has not supported this rejection with the appropriate level of substantial evidence or fact-based reasoning to make a *prima facie* case. *In re Zurko,* 59 U.S.P.Q.2d 1693; *In re Lee*, 61 U.S.P.Q.2d 14. Accordingly, the

rejection fails all three parts of the test for a *prima facie* case of obviousness, and Applicants again request its withdrawal.

3. Rejection of Claims 49-61 over Tripier et al. (U.S. Patent No. 5,322,926) in view of Allary or Lorne, Hanada, Brezniak, and Altshuler

Finally, the Office rejects claims 49-61 over Tripier in combination with either Allary or Lorne, and all of Hanada, Brezniak, and Altshuler. (Office Action at pages 11-12.)

Applicants have discussed the teachings of Allary, Lorne, Hanada, Brezniak, and Altshuler above. The combination with Tripier suffers from all of the same problems as the combination of those 5 publications on their own. Again, as the courts have explained, an obviousness rejection cannot be based on unknown, inherent properties for the simple reason that what is not known cannot be obvious. *In re Shetty, supra.* The Office does not assert that Tripier provides any suggestion that a thrombin preparation with the ingredients claimed would have the functional properties required by any of claims 49-61. Indeed, Tripier discusses thrombin inhibitors from the hirudin family and their isolation and use, and does not mention preparations for storing thrombin.

Hence, Tripier, in combination with all of the other cited art, cannot render any of claims 49-61 obvious, and Applicants request the withdrawal of this rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not otherwise found attached hereto to our deposit account 06-0916.

Respectfully submitted,

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